

Changes in the sense of balance correlate with concentrations of m-xylene in venous blood

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ABSTRACT Nine healthy male volunteers were exposed to m-xylene for four hours a day, three hours in the morning and one hour in the afternoon, with a 40 minute break in between, at six day intervals during six succeeding weeks to explore the effects of m-xylene on the sense of balance. The atmospheric m-xylene concentrations were either fixed at 8.2 $\mu\text{mol/l}$ (200 ppm) or they fluctuated (5.2–16.4 $\mu\text{mol/l}$; 135–400 ppm) with peaks of 16.4 $\mu\text{mol/l}$ and duration of 10 minutes at the beginning of each exposure session. The subjects were sedentary or exercised at 100 W for 10 minutes at the time of the peaks. The two control days, with and without exercise, were similar to the exposure days but without exposure. Body sway was measured with the subjects' eyes open and closed before they entered the chamber and in the chamber immediately after the cessation of the peak exposure when blood samples for gas chromatographic analysis were also drawn. Changes in the eyes closed/open ratio of the average and maximal body sway along the sagittal and lateral axes were calculated using the morning value as a reference. Changes in the eyes closed/open ratios of both average and maximal body sway correlated positively with blood m-xylene concentrations during fixed (8.2 $\mu\text{mol/l}$) exposure at rest and during fluctuating exposure combined with exercise as analysed with linear regression analysis. The results suggest that m-xylene has a dose related effect on the sense of balance at moderate atmospheric levels.

Exposure to various benzene homologues such as toluene, xylene, ethylbenzene, and styrene is common at work. Improvements in industrial hygiene have decreased the concentrations of solvents in the air of workplaces but it is not unusual, even though time weighted average (TWA) concentrations of solvents of the entire working day are below threshold limit values (TLVs), to find occasional high ambient air solvent concentrations. Therefore, TWA concentrations may give a limited picture of the true exposure pattern in the occupational setting.¹ Since the possible adverse effects are induced by the solvent in the body, not in the air, monitoring of biological samples probably gives a more reliable picture of biologically significant exposure than the monitoring of the atmosphere.^{2,3}

Air solvent concentrations may fluctuate widely during a working day. Moreover, increased lung ven-

tilation and cardiac output due to physical exercise may induce considerable increases in the blood and tissue solvent concentrations.⁴⁻⁷ Diurnal variation may also modify the effects of solvents on psychophysiological functions.⁸ Confounding factors such as these may have been why attempts to find a dose effect relation between venous blood solvent concentrations and changes in psychological function under experimental conditions, especially at low or moderate atmospheric solvent concentrations, have failed.

We have studied the effects of m-xylene, the predominant xylene isomer, on the sense of balance at rest and during exercise at fixed, and during fluctuating, exposure in an attempt to find a dose-effect relation between venous blood m-xylene concentrations and changes in the sense of balance.

Material and methods

SUBJECTS

The subjects were healthy male volunteers with an

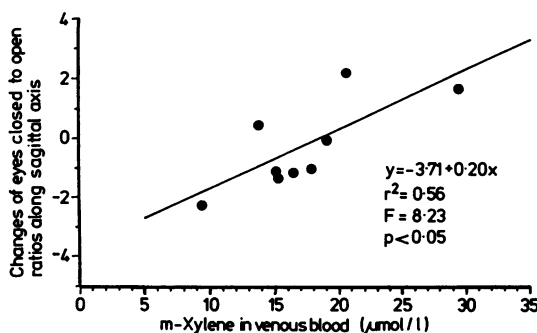


Fig 1 Regression of changes of eyes closed/open ratios of maximal body sway along sagittal axis on blood m-xylene concentrations in morning during fixed (8.2 µmol/l) exposure at rest.

average age of 21, average height of 185 cm, and average weight of 74 kg. The study was conducted according to the principles of informed consent (Declaration of Helsinki (rev) Tokyo 1975) and was approved by the ethical committee of the Institute of Occupational Health. Before the study, each subject underwent a careful medical and neurological examination including electroencephalography and electronystagmography; no abnormalities were found. Chest x ray, electrocardiogram, and all clinical chemical investigations gave results within normal limits. None of the subjects had a history of any neurological disease or used any drugs during the study. The use of alcohol was prohibited on the evening preceding an experimental day; all the subjects were social drinkers.

EXPOSURES AND EXPERIMENTAL DESIGN

The exposures to m-xylene (laboratory grade, Merck,

FRG) were carried out in a 15 m³ exposure chamber with a dynamic controlled environment. The concentration of m-xylene was always kept within 5% of the desired value and was continuously monitored with an infrared analyser (Miran 1 A, Wilks Scientific Corporation, USA) and automatically controlled with a Eurotherm 070 industrial processor (Eurotherm Ltd, England). The temperature was kept at $23 \pm 2^\circ\text{C}$.⁹ The subjects were divided into groups of three and were exposed in a balanced order to neutralise the effect of learning.¹⁰ One of the volunteers was occasionally absent with a cold so that the number of subjects varied between eight and nine (figs 1–4). The exposures, four hours a day, three hours in the morning and one hour in the afternoon with a 40 minute break in between, were performed over six consecutive weeks with a six day interval between exposures. The experiments were single blind with a crossover design, the subjects acting as their own controls. The odour of the solvent was masked with peppermint oil vapour (about 1 ppm).

On each experimental day the zero (base line) tests were made between 0800 and 0830. The subjects entered the chamber at 0900 and stayed there until noon. Thereafter they had a 40 minute break during which a standard meal was served. After the break the subjects spent one additional hour in the chamber in the afternoon and came out at 1340. The TWA concentration during the exposures was always the same, 8.2 µmol/l (200 ppm).

The subjects were exposed on two separate days to a fixed (8.2 µmol/l) concentration of m-xylene. They were either sedentary or exercised at 100 W for 10 minutes after the beginning (5 minutes) of each session. On the two other exposure days, the ambient air m-xylene concentration fluctuated between 5.2 and 16.4 µmol/l (135–400 ppm). At the beginning of each

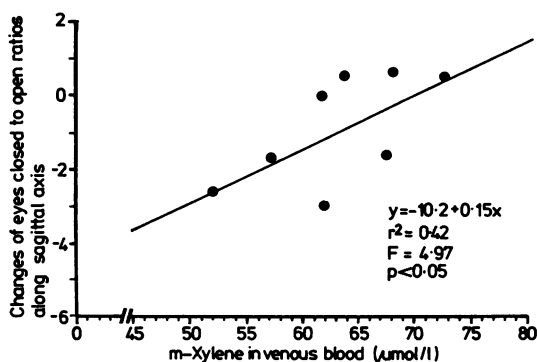


Fig 2 Regression of changes of eyes closed/open ratios of maximal body sway along sagittal axis on blood m-xylene concentrations in morning during peak exposure combined with exercise.

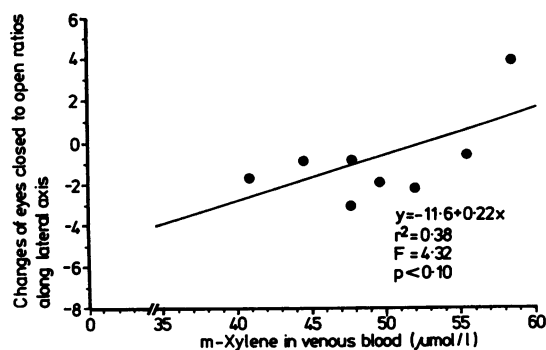


Fig 3 Regression of changes of eyes closed/open ratios of maximal body sway along lateral axis on blood m-xylene concentrations in morning during peak exposure combined with exercise.

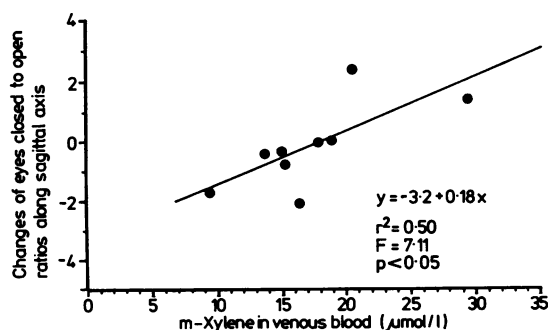


Fig 4 Regression of changes of eyes closed/open ratios of average body sway along sagittal axis on blood m-xylene concentrations in morning during fixed ($8.2 \mu\text{mol/l}$) exposure at rest.

session, the concentration of m-xylene in the air was raised from $5.2 \mu\text{mol/l}$ to $16.4 \mu\text{mol/l}$ over five minutes, kept there for 10 minutes, and then decreased to $5.2 \mu\text{mol/l}$ during the following five minutes. The subjects were either sedentary or exercised during the peaks at 100 W (fig 5). The two control days, with and without exercise, were similar to the exposure days but without exposure.

METHODS AND STATISTICAL TREATMENT OF THE DATA

Body sway (in mm) was measured with a strain gauge transducer platform.¹¹ Before the study, the subjects practised with the test until their performance was stable. Body sway was measured before the subjects entered the chamber and about 15–20 minutes after the beginning of each session in the chamber, in all three times a day. Average and maximal body sway¹² were measured with the subjects' eyes open and closed along the sagittal (anteroposterior) and lateral axes. The eyes closed/open ratio of these measures was also calculated, and the changes along both the sagittal and lateral axes were calculated for each day and each time separately using the pre-chamber (base line) value as a reference. The changes on control days (with and without exercise) were subtracted from the changes at the corresponding time on the exposure day in order to correct for normal diurnal varia-

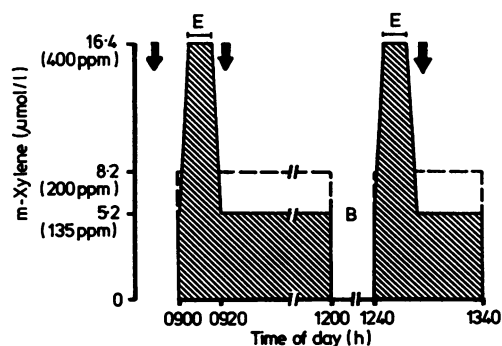


Fig 5 Exposure patterns under different experimental conditions. Shaded areas indicate exposure to fluctuating atmospheric concentrations of m-xylene (5.2 – $16.4 \mu\text{mol/l}$; 135 – 400 ppm), areas surrounded by dotted line show exposure to a fixed concentration of $8.2 \mu\text{mol/l}$ (200 ppm). Arrows indicate measurement of body sway, and E (underlined) indicates time of physical exercise (100 W for 10 minutes).

tion.^{13 14} The relation between the corrected changes in the eyes closed/open ratios of average and maximal body sway along both axes and m-xylene in venous blood was analysed using linear regression. The multiple correlation coefficient (r^2) was computed and the statistical significance of the regression model was tested with an F-test.¹⁵

Venous blood samples were drawn from an antecubital vein at the same time that a sway test was carried out and analysed for m-xylene by gas chromatography.^{9 16} The micromolar range of the venous blood m-xylene concentrations under the different experimental conditions is shown in table 1 (previously published partly elsewhere¹⁷).

Results

The eyes closed/open ratios of the average and maximal body sway appeared to be sensitive to the effects of m-xylene. Changes in the eyes closed/open ratios of maximal body sway were positively correlated with the blood m-xylene concentrations in the morning during fixed exposure to $8.2 \mu\text{mol/l}$ of solvent along both sagittal and lateral axes at rest and with the fluctuating exposure combined with exercise in the

Table 1 Blood m-xylene concentrations ($\mu\text{mol/l}$) during different experimental conditions. The range of individual blood m-xylene concentrations is given in the morning and in the afternoon. (Number of subjects was eight or nine)

Time of exposure	Fixed $8.2 \mu\text{mol/l}$ of m-xylene		Fluctuating 5.2 – $16.4 \mu\text{mol/l}$ of m-xylene	
	At rest	During exercise	At rest	During exercise
Morning	9.3–29.4	24.7–58.3	15.6–37.8	40.8–58.4
Afternoon	19.3–31.9	32.9–50.6	21.8–52.3	51.8–72.5

Table 2 Summary of the tests of significance of regression coefficients of the changes of eyes closed/open ratios of body sway on blood m-xylene concentrations under different experimental conditions

Parameter	Axis	Rest				Exercise			
		Stable		Fluctuating		Stable		Fluctuating	
		Morning	Afternoon	Morning	Afternoon	Morning	Afternoon	Morning	Afternoon
Ratios of maximal	Body sway								
	Sagittal	↑	—	—	—	—	—	↑	(†)
	Lateral	(†)	—	—	—	—	—	(†)	—
Ratios of average	Body sway								
	Sagittal	↑	—	—	—	—	—	—	(†)
	Lateral	—	(†)	—	—	—	—	(†)	—

↑ Indicates $p < 0.05$; (†) Indicates $p < 0.10$; — Indicates that test was not statistically significant.

morning and in the afternoon. In the latter case the regression was not always statistically significant (figs 1–3). The changes in the eyes closed/open ratio of the average body sway were also positively correlated with the blood m-xylene concentration in the morning during fixed exposure at rest (fig 4) and in the morning and in the afternoon during fluctuating exposure combined with exercise (table 1). The blood solvent levels in the morning during fixed exposure at rest varied between 9.3 and 29.4 $\mu\text{mol/l}$. The concentrations during fluctuating exposure combined with exercise were 40.8–58.4 $\mu\text{mol/l}$ in the morning and 51.8–72.5 $\mu\text{mol/l}$ in the afternoon (table 1). The relation between ratios of body sway and the blood m-xylene concentrations are summarised in table 2.

Discussion

Dose related effects between concentrations of solvents in venous blood and changes in psychophysiological function in man after experimental short term exposure to low or moderate atmospheric concentrations have not been reported. Observing dose-effect relations at such ambient air solvent concentrations in man is difficult but not impossible if varied exposure patterns¹⁸ combined with different levels of physical exercise,¹⁹ appropriate blood sampling intervals,²⁰ and valid and sensitive methods are used.^{10, 21–23} When exploring dose-effect relations in the lower part of the dose-response curve one may assume that the curve behaves linearly.²⁴ This is the case when the effects of atmospheric solvent concentrations, likely to be encountered at work, on psychophysiological functions are studied.

This study was designed to show dose-effect relations between internal exposure to m-xylene and changes in the sense of balance by creating experimental conditions capable of inducing great inter-individual variation in the concentrations of m-xylene in the venous blood. It is probable that brain m-xylene concentrations paralleled those found in the

blood.²⁵ Rather larger differences are usually needed to show even slight dose related effects.²⁴ The results of the present study show that exposure to atmospheric m-xylene concentrations, likely to be encountered at work, may produce blood m-xylene concentrations (10–73 $\mu\text{mol/l}$) are capable of inducing dose related effects on the sense of balance, especially if physical exercise is occasionally combined with the exposure. The results also suggest that central regulatory rather than visual system disturbances are involved in this impairment.^{13, 26} The use of the eyes closed/open ratio improves the signal to noise ratio by decreasing the noise induced by the movements of the leg muscles on the strain gauge transducer platform¹¹ and may thus increase the sensitivity and stability of the method.

The results summarised in table 2 suggest that exercise counteracted the effects of m-xylene on the sense of balance and that only fairly high atmospheric concentrations combined with exercise were able to induce blood concentrations (see table 1) sufficiently high to overcome this possible arousal induced counteracting effect; this is in agreement with our earlier observations.^{19, 27} When the equations of the regression lines are studied in detail (figs 1–4), the results are also in agreement with the earlier findings that exposure to atmospheric m-xylene concentrations of 4.1–8.2 $\mu\text{mol/l}$ may improve some parameters of body sway.⁸

The results emphasise the importance of biological monitoring of people exposed to solvents in predicting the effects of exposure.^{1, 3, 7} Unpredictable changes of physical activity, development of rapid functional tolerance,^{8, 28} and unknown changes of exposure conditions may all confound the effects of m-xylene or other solvents on psychophysiological functions in the occupational environment. The fact that the present venous blood m-xylene concentrations are obviously at the lower sigmoid part of the dose-response curve may partially explain the lack of correlation in several cases.²⁴

A notable finding was that short term exposure to atmospheric levels of m-xylene, similar to those found in the workplace, produced concentrations of the solvent in venous blood that impaired the body sense of balance in a dose dependent manner. The working ability of health workers is probably not disturbed by these effects but they may be considered as an indication that some change has taken place in the functioning of the central nervous system.

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